ONE-POT *CIS*-SELECTIVE ROUTE TO SUGAR-FUSED THIAZINES VIA MASKING-UNMASKING STRATEGY IN BASIC IONIC LIQUID

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Abstract: A novel sequential Knoevenagel condensation, thia-Michael and amino/mercaptoacetylative ring transformation reaction cascade for *cis*-selective synthesis of sugar-fused 1,3-thiazine is reported. The expeditious one-pot multicomponent annulation was performed using masked amino acid viz. 2-phenyl-1,3-oxazol-5-one or masked mercaptoacid viz. 2-methyl-2-phenyl-1,3-oxathiolan-5-one, D-xylose/D-glucose and N-aryldithiocarbamic acid in ionic liquid [bmim]OH. The acetophenone obtained as a by-product and [bmim]OH itself, could be easily recycled for further use without loss of efficiency. The envisaged method is operationally simple, high yielding and excellent diastereoselective in favor of *cis*-isomer of fused thiazines.

Keywords: carbohydrates, [bmim]OH, stereoselectivity, sugar, 1,3-thiazines.

Introduction: Sugars incorporating intracyclic sulfur atom (thiosugars) and endocyclic nitrogen atom (iminosugars) are of considerable interest since the discovery of their biological activity as glycosidase inhibitors in 1970's.[1] Many naturally occurring thiosugars are potential targets for the carbohydrate-based therapeutics, such as thiolactomycin, salacinol, kotalonol, tagetioxin and mycothiol.[2,3] Furthermore, sugar mimics with endocyclic nitrogen are arousing a great interest as potential therapeutic agents against HIV infection, cancer, diabetes and other genetic and metabolic disorders due to their powerful interference with glycosidase as well as glycotransferases.[4-7] 1,3-thiazine nucleus is the active core of cephalosporins, which are among the most widely used β-lactam antibiotics and its derivatives possess remarkable biological activities such as antibacterial, antitumour, insecticidal and fungicidal.[8-10] Thus, heterocyclic system resulting from the annulations of 1,3-thaizines on biologically versatile imino- and thiosugars would provide not only an attractive scaffold for exploiting chemical diversity but also the presence of several free hydroxyl groups render them water soluble and biodegradable. Inspired by these valid literature reports and in continuation of our ongoing work on methodology development,[11] especially using carbohydrates,[12] herein, we report an original

and green route to iminosugar annulated 1,3-thiazines **7** and **8** as well as thiosugar annulated 1,3-thiazines **14** and **15** using masked amino acid, 2-phenyl-1,3-oxazolan-5-one **2** and masked mercapto acid, 2-methyl-2-phenyl-1,3-oxathiolan-5-one **3** respectively with D-xylose and D-glucose as renewable feedstock (Scheme 1).

Results and discussion: Initial retrosynthetic study revealed to construct 5-amino-/5-mercapto-1,3-thiazine containing a sugar chain, which would underwent intramolecular ring transformation affording the imino-/thiosugar annulated 1,3-thiazines (Scheme 2). Limited efforts have been made for synthesis of 1,3-thiazines using α,β-unsaturated carbonyl systems.[8,9,12-14] As required, we designed enones containing sugar chain (**6** and **11**), which could not only introduce a –SH and –NHR group but also install a sugar tail to annulate the aza-/ and thiosugar in 1,3-thiazine skeleton. For this purpose, we tried glycine and mercaptoacetic acid in the present synthetic protocol for construction of the designed α,β-unsaturated carbonyl building block (**6** and **11**), but were unsuccessful, probably due to the presence of free –SH and $–CO_2H$ groups in mercapto acid and $–NH_2$ and $–CO_2H$ in glycine. Then, we activated their methylene groups by converting into masked amino acid, 2-phenyl-1,3-oxazolan-5-one and masked mercapto acid, 2-methyl-2-phenyl-1,3-oxathiolan-5-one (Scheme 3)[15] respectively. These activated amino-/ and mercapto acids not only served the purpose as aminoacetyl and mercaptoacetyl transfer agent respectively in the present synthetic protocol, but also provided a completely new route for synthesis of target imino/- and thiosugar annulated 1,3-thiazines, which is hitherto unreported and are not accessible through any one of the known synthetic routes for the target compounds (Scheme 1).

At the outset, we investigated the optimization of reaction conditions regarding the catalyst and solvent both. For this purpose, D-xylose **1** (n = 3), 2-phenyl-1,3-oxazolan-5-one **2** and dithiocabamic acid **4** (Ar = Ph) were chosen as model substrates for the synthesis of representative compound **7a** (Table 1). First, we screened various ionic liquids as catalyst and CH_3CN as solvent for the present reaction. Surprisingly, the reaction took place with all ILs, and [bmim]Br was found the best among all

(Table 1, entries 1-3). However, yields were not satisfactory. With the hope of increasing yield, we tried the reaction in other solvents such as THF, MeOH and 1,4-dioxne using [bmim]Br as catalyst. Although, among MeOH, CH_3CN, THF and 1,4-dioxne, THF was found to be the best solvent, but there was no satisfactory increase in the yield (Table 1, entries 1, 4-6). This indicated that [bmim]Br was not an efficient catalyst for the present reaction. Then, we turned our attention to use a basic IL [bmim]OH as a catalyst, which evidenced its catalytic efficacy in the reaction affording **7a** in excellent yield (Table 1, entry 9). This is in conformity with the earlier report on [bmim]OH-catalyzed Knoevenagel condensation-ring transformation reactions.[16] In addition, several imidazolium-based ILs were tested by varying their alkyl substituents and [bmim]OH was found to be the most effective catalyst (Table 1, entries 7-9).

The optimum catalyst loading for [bmim]OH was found to be 15 mol%. When the amount of the catalyst decreased to 10 mol% from 15 mol% relative to substrates, the yield of the product **7a** reduced and more time was required to complete the reaction (Table 1, entries 9 and 13), but the use of 20 mol% did not affect the yield (Table 1, entries 9 and 14). However, the reaction did not occur without using a catalyst (Table 1, entry 15). Optimization of the solvent for the synthesis of **7a** using [bmim]OH was also undertaken and it was found that amongst MeOH, CH_3CN, THF and 1,4-dioxane (Table 1, entries 9-12), the best solvent in terms of yield and reaction time was THF (Table 1, entry 9). It was noted that a higher reaction temperature, for example, in a refluxing solvent instead of at rt, has no any appreciable effect on the yield. In the same way we also performed a controlled reaction taking masked mercapto acid and compound **14a** was synthesized using the same protocol optimized for **7a**. The [bmim]OH was prepared employing the known method.[17] Usually imidazolium salts undergo deprotonation in the presence of strong bases such as KH, NaH, LDA, KHMDS or DABCO and affords N-heterocyclic carbenes.[18] However, the ionic liquid [bmim]OH is highly stable during the reaction process[19] under ambient conditions and can be used in reactions without any difficulty.[17] The

stability and catalytic efficiency of [bmim]OH is furthermore evidenced by a variety of reactions viz., Henry,[20] Knoevenagel,[16] Michael,[17] and Mannich reaction[21] etc. reported in literature.

With the aim to establish its solvent-free version and to compare the synthetic efficiency, a model experiment was carried out at 90 ^{o}C in a microwave (Chemical Laboratory Microwave Oven, Model; BP-310/50, 23o volt, 50 Hz power input). Various mineral catalysts were screened for the formation of **7a** at 90 ^{o}C. Among the catalysts tested, K-10 clay gave the best result (Table 2, entry 3). $CeCl_3.7H_2O$ and $CeCl_3$**.**$7H_2O$/NaI-system afforded the product **7a** in moderate yields (Table 2, entries 1-2), while poor yields of **7a** was obtained in the case of silica gel and neutral or acidic alumina (Table 2, entries 4-6). Moreover, the reaction did not take place using basic alumina (Table 2, entry 7) as well as in the absence of catalyst (Table 2, entry 8). It was observed that significantly lower yield of **7a** was obtained in solvent-free condition (Table 2, entry 3) rather than its [bmim]OH catalyzed version (Table 1, entry 9). Thus, [bmim]OH stands out as the choice, with its fast conversion and quantitative yield of the target compound in the present investigation. Next, in order to investigate the substrate scope for the general validity of the present investigation, a variety of dithiocarbamic acids **4** and sugars **1** by varying the masked acids, were used employing the present optimized reaction conditions and different imino- and thiosugar annulated 1,3-thiazines were synthesized (Table 3). The yields were consistently good and excellent diastereoselctivity were achieved in favor of *cis* isomer (Table 3).

Thus, the present optimized synthesis for the target imino-/ and thiosugar annulated 1,3-thiazines (**7**, **8** and **14**, **15**) was successful by stirring a mixture of D-xylose/D-glucose **1**, 2-phenyl-1,3-oxazolan-5-one **2** or 2-methyl-2-phenyl-1,3-oxathiolan-5-one **3**, dithiocarbamic acid **4** and [bmim]OH **5** in THF at room temperature for 6.5-8 h (Table 3). The pure products **7**, **8** and **14**, **15** were extracted with ether leaving the [bmim]OH behind which can be recycled easily for further use without loss of efficiency (Table 4). Isolation and purification by flash chromatography on silica gel using hexane-

EtOAc (8:2) as elluent, afforded **7**, **8** and **14**, **15** in 84-93% yields with >94% diastereoselectivity (Table 3) in favor of isomer with *cis* ring junction as determined by ^{1}H NMR spectroscopy.

The ring transformation step involves the intramolecular nucleophilic substitution via displacement of hydroxide occurs with inversion of configuration, which is supported by coupling constant between H-6 and H-7 of synthesized compounds. In products **7**, **8** and **14**, **15**, the rings are *cis* fused as indicated by the coupling constants of ring junction protons 4a-H and 8a-H ($J_{4a,8a}$=4.3-4.8 Hz). At *cis*-junctions of compounds **7**, **8**, **14** and **15**, 4a-H is equatorial and 8a-H is axial, as indicated by their coupling constant (for example **14a**; $J_{4aH,8aH}$ = 4.5 Hz, J_{cis} and $J_{8aH,8H}$ = 7.5 Hz, J_{trans}). The *cis* stereochemistry was also supported by NOE interaction experiments. For example, 11.1% and 12.4 NOEs were observed between 4a-H and 8a-H in products **7a** and **14a**, respectively, indicating that the 4a-H and 8a-H are located on the same face of the molecule, hence confirming the *cis* fusion of the rings. The chiral carbons of the precursor carbohydrates retain their configuration in the product if they are not involved in any bond breaking/formation. The reactions were clean and all the synthesized products were characterized by their ^{1}H NMR, ^{13}C NMR, IR and mass spectroscopic data.

The formation of imino- and thiosugar annulated 1,3-thiazines **7**,**8** and **14**,**15** can be rationalized by initial [bmim]OH catalyzed Knoevenagel condensation between D-xylose or D-glucose and masked acids **2** or **3** followed by Michael type addition of *N*-aryldithiocarbamic acid **4** to arylidenes **6** or **11** respectively, generated in situ, to afford the corresponding thia-Michael adducts **10** or **12**. These thia-Michael adducts undergo intramolecular nucleophilic attack of the nitrogen atom of the NHAr group of **4** at the carbonyl carbon (C-5) of the masked acid **2** or **3** to yield the target compounds **7**,**8** (Scheme 4) and **14**,**15** (Scheme 5). This conclusion is based on the observation that the representative intermediate compounds **9a** (*n*=3, Ar=Ph) and **12a** (*n*=3, Ar=Ph) could be isolated in 46% and 49% yield respectively, these could be converted into the corresponding thiazines **7a** and **14a** in quantitative yields. Presumably, the ring transformation step is promoted by [bmim]OH owing to

the acidic character of C-2 proton of the imidazolium cation in the reaction by polarizing the carbonyl group of the adduct **9** or **12**, thereby enhancing the electrophilicity of the carbonyl carbon, which facilitates the nucleophilic attack of the NHAr of **4**. Furthermore, the imidazolium hydroxide perhaps helps in increasing the nucleophilicity of **2** or **3** via formation of **2´** or **3´** (Scheme 6) while, in case of ionic liquids with halide ion and other solvents, the mechanism seems to be operated via enol form of the masked amino acid **1**, stabilized by imidazolium moiety.

In conclusion, we report for the first time a general, efficient and green method for preparation of synthetically and pharmaceutically important imino- and thiosugar annulated 1,3-thiazines using D-xyolose and D-glucose, as bio-renewable feedstock. The developed methodology opens up a conceptually new aspect for sugar annulated 1,3-thiazine chemistry and would be a good alternative to the existing procedures for such fine chemicals to cater the need of industries and academia.

Experimental

Reagents were obtained from commercial suppliers, and used without further purification unless otherwise specified by a reference. All reactions were performed using oven-dried glassware. Melting points were determined by open glass capillary method and are uncorrected. IR spectra in KBr were recorded on a Perkin-Elmer 993 IR spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker WM-40 C (400 MHz) FT spectrometer in DMSO-d_6/D_2O using TMS as internal reference. ^{13}C NMR spectra were recorded on the same instrument at 100 MHz in DMSO-d_6 and TMS was used as internal reference. Mass (EI) spectra were recorded on a JEOL D-300 mass spectrometer. Elemental analyses were carried out in a Coleman automatic carbon, hydrogen and nitrogen analyzer. A Chemical Laboratory Microwave Oven (Model; BP-310/50, 230 volt, 50 Hz power input) was used. All chemicals used were reagent grade and were used as received without further purification. Silica gel-G was used for TLC.

General procedure for the synthesis of iminosugar annulated 1,3-thiazines 7, 8 and thiosugar annulated 1,3-thiazines 14 and 15

A mixture of D-xylose/D-glucose **1** (5.0 mmol), 2-methyl-2-phenyl-1,3-oxathiolan-5-one **2** (5.0 mmol) or 2-phenyl-1,3-oxazolan-5-one **3** (5.0 mmol), *N*-aryldithiocarbamic acid **4** (5.0 mmol), [bmim]OH **5** (0.75 mmol) in 15 mL THF was stirred at room temperature for 6.5-8 h. After completion of the reaction as indicated by TLC, the product was extracted with ether (3 × 15 mL). The combined ether extracts were dried over anhydrous sodium sulfate and evaporated under reduced pressure to leave the crude product, which was recrystallized from ethanol to afford a diastereomeric mixture >94:<6 of **7**, **8** or **14**, **15** in favor of *cis* isomer (in the crude products, the ratio was >92:<8) as determined by the ^{1}H NMR spectroscopy (Table 3). The product on second recrystallization from ethanol furnished an analytical pure sample of a single diastereomer **7**, **8** or **14**, **15**. The *cis* stereochemistry was assigned to **7**, **8** or **14**, **15**, as the coupling constant ($J_{3a,7a}$ = 4.3–4.8 Hz) of the major *cis* diastereomer was lower than that for minor *trans* diastereomer ($J_{3a,7a}$ = 11.4 Hz). After isolation of the product, the remaining aqueous layer containing the ionic liquid was washed with ether (15 mL) to remove any organic impurity, dried under vacuum at 90 ^{o}C to afford [Bmim]OH, which was used in subsequest runs without further purification (Table 4).

Compound **7a:** R_f (15% EtOAc/hexane) 0.52. IR (KBr) υ_{max} 3351, 3325, 3011, 1685, 1605, 1584, 1455, 1055 cm^{-1}. ^{1}H NMR (DMSO-d_6 + D_2O/TMS) δ: 3.17 (ddd, $J_{6H,7H}$ = 9.8 Hz, $J_{6H,1'Ha}$ = 6.3 Hz, $J_{6H,1'Hb}$ = 3.2 Hz, 1 H, H-6), 3.49 (dd, $J_{1'Ha,Hb}$ = 11.2 Hz, $J_{6H,1'Ha}$ = 6.3 Hz, 1 H, Ha-1'), 3.78 (dd, $J_{6H,7H}$ = 9.8 Hz, $J_{7H,8H}$ = 9.1 Hz, 1 H, H-7), 3.92 (dd, $J_{1'Ha,Hb}$ = 11.2 Hz, $J_{6H,1'Hb}$ = 3.2 Hz, 1 H, Hb-1'), 4.08 (dd, $J_{7H,8H}$ = 9.1 Hz, $J_{8H,8aH}$ = 7.6 Hz, 1 H, H-8), 5.01 (dd, $J_{8H,8aH}$ = 7.6 Hz, $J_{4aH,8aH}$ = 4.3 Hz, 1 H, H-8a), 6.16 (dd, $J_{4aH,8aH}$ = 4.3 Hz, 1 H, H-4a), 7.18-7.73 (m, 10 H_{arom}). ^{13}C NMR (DMSO-d_6/TMS) δ: 29.9, 48.7, 51.8, 63.5, 71.4, 83.1, 125.8, 126.9, 128.1, 129.3, 131.5, 132.1, 133.8, 134.5, 170.7, 173.8, 192.2.

Mass (*m/z*): 445 (MH^+). Anal. Calcd for $C_{21}H_{20}N_2O_5S_2$: C, 56.74; H, 4.53; N, 6.30%. Found: C, 56.99; C, 4.31; N, 6.18%.

Compound **7b:** R_f (15% EtOAc/hexane) 0.49. IR (KBr) υ_{max} 3353, 3321, 3009, 1688, 1608, 1588, 1450, 1051 cm^{-1}. ^1H NMR (DMSO-d_6 + D_2O/TMS) δ: 3.15 (ddd, $J_{6H,7H}$ = 9.8 Hz, $J_{6H,1'Ha}$ = 6.5 Hz, $J_{6H,1'Hb}$ = 3.3 Hz, 1 H, H-6), 3.48 (dd, $J_{1'Ha,Hb}$ = 11.5 Hz, $J_{6H,1'Ha}$ = 6.5 Hz, 1 H, Ha-1'), 3.77(dd, $J_{6H,7H}$ = 9.8 Hz, $J_{7H,8H}$ = 9.3 Hz, 1 H, H-7), 3.94 (dd, $J_{1'Ha,Hb}$ = 11.5 Hz, $J_{6H,1'Hb}$ = 3.3 Hz, 1 H, Hb-1'), 4.05 (dd, $J_{7H,8H}$ = 9.3 Hz, $J_{8H,8aH}$ = 7.7 Hz, 1 H, H-8), 5.03 (dd, $J_{8H,8aH}$ = 7.7 Hz, $J_{4aH,8aH}$ = 4.3 Hz, 1 H, H-8a), 6.12 (dd, $J_{4aH,8aH}$ = 4.3 Hz, 1 H, H-4a), 7.18-7.59 (m, 7 H_{arom}), 7.63-7.85 (m, 2 H_{arom}). ^{13}C NMR (DMSO-d_6/TMS) δ: 31.2, 49.1, 51.5, 63.8, 71.5, 83.3, 126.5, 127.3, 128.2, 129.1, 129.8, 130.5, 131.3, 134.2, 170.2, 173.5, 192.1. Mass (*m/z*): 479 (MH^+). Anal. Calcd for $C_{21}H_{19}ClN_2O_5S_2$: C, 52.66; C, 4.00; N, 5.85%. Found: C, 52.33; H, 4.17; N, 5.59%.

Compound **7c:** IR (KBr) υ_{max} 3349, 3328, 3015, 1687, 1597, 1581, 1449, 1057 cm^{-1}. ^1H NMR (DMSO-d_6 + D_2O/TMS) δ: 3.19 (ddd, $J_{6H,7H}$ = 9.7 Hz, $J_{6H,1'Ha}$ = 6.3 Hz, $J_{6H,1'Hb}$ = 3.1 Hz, 1 H, H-6), 3.45 (dd, $J_{1'Ha,Hb}$ = 11.8 Hz, $J_{6H,1'Ha}$ = 6.3 Hz, 1 H, Ha-1'), 3.69 (s, 3H, OMe), 3.79 (dd, $J_{6H,7H}$ = 9.7 Hz, $J_{7H,8H}$ = 9.1 Hz, 1 H, H-7), 3.93 (dd, $J_{1'Ha,Hb}$ = 11.8 Hz, $J_{6H,1'Hb}$ = 3.1 Hz, 1 H, Hb-1'), 4.09 (dd, $J_{7H,8H}$ = 9.1 Hz, $J_{8H,8aH}$ = 7.5 Hz, 1 H, H-8), 5.02 (dd, $J_{8H,8aH}$ = 7.5 Hz, $J_{4aH,8aH}$ = 4.5 Hz, 1 H, H-8a), 6.15 (dd, $J_{4aH,8aH}$ = 4.5 Hz, 1 H, H-4a), 7.17-7.81 (m, 9 H_{arom}). ^{13}C NMR (DMSO-d_6/TMS) δ: 30.5, 48.4, 51.3, 54.7, 63.1, 71.2, 83.9, 125.8, 126.6, 127.3, 128.1, 129.2, 130.1, 131.3, 133.9, 170.1, 173.9, 192.5. Mass (*m/z*): 475 (MH^+). Anal. Calcd for $C_{22}H_{22}N_2O_6S_2$: C, 55.68; H, 4.67; N, 5.90%. Found: C, 55.89; C, 4.30; N, 6.21%.

Compound **8a:** R_f (15% EtOAc/hexane) 0.47. IR (KBr) υ_{max} 3357, 3320, 3019, 1688, 1605, 1585, 1455, 1055 cm^{-1}. ^1H NMR (DMSO-d_6 + D_2O/TMS) δ: 3.21 (ddd, $J_{6H,1'H}$ = 6.3 Hz, $J_{1'H,2'Ha}$ = 5.9 Hz, $J_{1'H,2'Hb}$ = 2.9 Hz, 1 H, H-1'), 3.32 (dd, $J_{6H,7H}$ = 9.9 Hz, $J_{6H,1'H}$ = 6.3 Hz, 1 H, H-6), 3.50 (dd, $J_{2'Ha,Hb}$ =

11.8 Hz, $J_{6H,1'Ha}$ = 5.9 Hz, 1 H, Ha-2'), 3.79 (dd, $J_{6H,7H}$ = 9.9 Hz, $J_{7H,8H}$ = 9.4 Hz, 1 H, H-7), 3.88 (dd, $J_{2'Ha,Hb}$ = 11.8 Hz, $J_{6H,1'Hb}$ = 2.9 Hz, 1 H, Hb-2'), 4.21 (dd, $J_{7H,8H}$ = 9.4 Hz, $J_{8H,8aH}$ = 7.3 Hz, 1 H, H-8), 4.95 (dd, $J_{8H,8aH}$ = 7.3 Hz, $J_{4aH,8aH}$ = 4.8 Hz, 1 H, H-8a), 6.21 (dd, $J_{4aH,8aH}$ = 4.8 Hz, 1 H, H-4a), 7.02-7.69 (m, 10 H_{arom}). ^{13}C NMR (DMSO-d_6/TMS) δ: 30.3, 41.3, 51.3, 70.8, 72.1, 77.6, 85.5, 126.8, 127.6, 128.3, 129.3, 131.5, 132.6, 133.3, 134.9, 170.8, 173.1, 192.1. Mass (*m/z*): 475 (MH^+). Anal. Calcd for $C_{22}H_{22}N_2O_6S_2$: C, 55.68; H, 4.67; N, 5.90%. Found: C, 55.37; C, 4.81; N, 6.08%.

Compound **8b:** R_f (15% EtOAc/hexane) 0.53. IR (KBr) υ_{max} 351, 3319, 3011, 1683, 1608, 1588, 1451, 1051 cm^{-1}. ^{1}H NMR (DMSO-d_6 + D_2O/TMS) δ: 3.20 (ddd, $J_{6H,1'H}$ = 6.5 Hz, $J_{1'H,2'Ha}$ = 5.7 Hz, $J_{1'H,2'Hb}$ = 3.1 Hz, 1 H, H-1'), 3.37 (dd, $J_{6H,7H}$ = 9.6 Hz, $J_{6H,1'H}$ = 6.5 Hz, 1 H, H-6), 3.53 (dd, $J_{2'Ha,Hb}$ = 12.0 Hz, $J_{6H,1'Ha}$ = 5.7 Hz, 1 H, Ha-2'), 3.77 (dd, $J_{6H,7H}$ = 9.6 Hz, $J_{7H,8H}$ = 9.1 Hz, 1 H, H-7), 3.86 (dd, $J_{2'Ha,Hb}$ = 12.0 Hz, $J_{6H,1'Hb}$ = 3.1 Hz, 1 H, Hb-2'), 4.23 (dd, $J_{7H,8H}$ = 9.1 Hz, $J_{8H,8aH}$ = 7.1 Hz, 1 H, H-8), 4.93 (dd, $J_{8H,8aH}$ = 7.1 Hz, $J_{4aH,8aH}$ = 4.7 Hz, 1 H, H-8a), 6.18 (dd, $J_{4aH,8aH}$ = 4.7 Hz, 1 H, H-4a), 7.13-7.65 (m, 7 H_{arom}), 7.69-7.81 (m, 2 H_{arom}). ^{13}C NMR (DMSO-d_6/TMS) δ: 31.8, 41.0, 51.7, 70.3, 72.5, 77.0, 85.1, 125.2, 126.7, 127.5, 128.3, 128.9, 130.8, 131.6, 133.5, 170.7, 173.5, 192.1. Mass (*m/z*): 509 (MH^+). Anal. Calcd for $C_{22}H_{21}ClN_2O_6S_2$: C, 51.91; H, 4.16; N, 5.50%. Found: C, 51.59; C, 4.41; N, 5.23%.

Compound **8c:** R_f (15% EtOAc/hexane) 0.56. IR (KBr) υ_{max} 3349, 3323, 3009, 1685, 1601, 1581, 1459, 1058 cm^{-1}. ^{1}H NMR (DMSO-d_6 + D_2O/TMS) δ: 3.24 (ddd, $J_{6H,1'H}$ = 6.1 Hz, $J_{1'H,2'Ha}$ = 5.9 Hz, $J_{1'H,2'Hb}$ = 2.8 Hz, 1 H, H-1'), 3.31 (dd, $J_{6H,7H}$ = 9.8 Hz, $J_{6H,1'H}$ = 6.1 Hz, 1 H, H-6), 3.49 (dd, $J_{2'Ha,Hb}$ = 11.9 Hz, $J_{6H,1'Ha}$ = 5.9 Hz, 1 H, Ha-2'), 3.69 (s, 3H, OMe), 3.78 (dd, $J_{6H,7H}$ = 9.8 Hz, $J_{7H,8H}$ = 9.5 Hz, 1 H, H-7), 3.85 (dd, $J_{2'Ha,Hb}$ = 11.9 Hz, $J_{6H,1'Hb}$ = 2.8 Hz, 1 H, Hb-2'), 4.20 (dd, $J_{7H,8H}$ = 9.5 Hz, $J_{8H,8aH}$ = 7.6 Hz, 1 H, H-8), 4.97 (dd, $J_{8H,8aH}$ = 7.6 Hz, $J_{4aH,8aH}$ = 4.7 Hz, 1 H, H-8a), 6.20 (dd, $J_{4aH,8aH}$ = 4.7 Hz, 1 H, H-4a), 7.11-7.81 (m, 9 H_{arom}). ^{13}C NMR (DMSO-d_6/TMS) δ: 32.2, 41.6, 51.1, 54.6, 70.1, 72.7, 77.3, 85.7, 127.8, 128.6, 129.5, 130.5, 131.8, 132.5, 133.9, 145.3, 170.2, 173.4, 192.8. Mass (*m/z*): 505

(MH^+). Anal. Calcd for $C_{23}H_{24}N_2O_7S_2$: C, 54.75; H, 4.79; N, 5.55%. Found: C, 54.87; C, 4.65; N, 5.29%.

Compound **14a:** R_f (15% EtOAc/hexane) 0.49. IR (KBr) υ_{max} 3353, 3321, 3017, 1688, 1599, 1588, 1450, 1049 cm^{-1}. ^1H NMR (DMSO-d_6 + D_2O/TMS) δ: 3.34 (ddd, $J_{6H,7H}$ = 9.7 Hz, $J_{6H,1'Ha}$ = 6.1 Hz, $J_{6H,1'Hb}$ = 3.5 Hz, 1 H, H-6), 3.49 (dd, $J_{1'Ha,Hb}$ = 11.7 Hz, $J_{6H,1'Ha}$ = 6.1 Hz, 1 H, Ha-1'), 3.79 (dd, $J_{6H,7H}$ = 9.7 Hz, $J_{7H,8H}$ = 9.2 Hz, 1 H, H-7), 3.95 (dd, $J_{1'Ha,Hb}$ = 11.7 Hz, $J_{6H,1'Hb}$ = 3.5 Hz, 1 H, Hb-1'), 4.06 (dd, $J_{7H,8H}$ = 9.2 Hz, $J_{8H,8aH}$ = 7.5 Hz, 1 H, H-8), 5.05 (dd, $J_{8H,8aH}$ = 7.5 Hz, $J_{4aH,8aH}$ = 4.5 Hz, 1 H, H-8a), 6.17 (dd, $J_{4aH,8aH}$ = 4.5 Hz, 1 H, H-4a), 7.09-7.76 (m, 5 H_{arom}). ^{13}C NMR (DMSO-d_6/TMS) δ: 26.5, 49.6, 50.9, 62.7, 77.4, 86.7, 127.9, 128.6, 129.4, 131.5, 170.2, 173.6, 192.8. Mass (*m/z*): 358 (MH^+). Anal. Calcd for $C_{14}H_{15}NO_4S_3$: C, 47.04; H, 4.23; N, 3.93%. Found: C, 46.72; C, 4.49; N, 4.27%.

Compound **14b:** R_f (15% EtOAc/hexane) 0.51. IR (KBr) υ_{max} 3357, 3319, 3021, 1691, 1605, 1591, 1448, 1055 cm^{-1}. ^1H NMR (DMSO-d_6 + D_2O/TMS) δ: 3.38 (ddd, $J_{6H,7H}$ = 9.9 Hz, $J_{6H,1'Ha}$ = 6.2 Hz, $J_{6H,1'Hb}$ = 3.4 Hz, 1 H, H-6), 3.47 (dd, $J_{1'Ha,Hb}$ = 11.3 Hz, $J_{6H,1'Ha}$ = 6.2 Hz, 1 H, Ha-1'), 3.82 (dd, $J_{6H,7H}$ = 9.9 Hz, $J_{7H,8H}$ = 9.5 Hz, 1 H, H-7), 3.92 (dd, $J_{1'Ha,Hb}$ = 11.3 Hz, $J_{6H,1'Hb}$ = 3.4 Hz, 1 H, Hb-1'), 4.03 (dd, $J_{7H,8H}$ = 9.5 Hz, $J_{8H,8aH}$ = 7.3 Hz, 1 H, H-8), 5.02 (dd, $J_{8H,8aH}$ = 4.5 Hz, $J_{4aH,8aH}$ = 7.3 Hz, 1 H, H-8a), 6.13 (dd, $J_{4aH,8aH}$ = 4.5 Hz, 1 H, H-4a), 7.12-7.62 (m, 2 H_{arom}), 7.71-7.79 (m, 2 H_{arom}). ^{13}C NMR (DMSO-d_6/TMS) δ: 26.1, 50.7, 51.3, 62.2, 77.0, 86.2, 126.8, 129.2, 130.1, 132.3, 135.2, 173.2, 192.3. Mass (*m/z*): 392 (MH^+). Anal. Calcd for $C_{14}H_{14}ClNO_4S_3$: C, 42.90; H, 3.60; N, 3.57%. Found: C, 43.27; C, 3.39; N, 3.72%.

Compound **14c:** R_f (15% EtOAc/hexane) 0.55. IR (KBr) υ_{max} 3352, 3327, 3013, 1683, 1601, 1585, 1458 and 1053 cm^{-1}. ^1H NMR (DMSO-d_6 + D_2O/TMS) δ: 3.36 (ddd, $J_{6H,7H}$ = 9.7 Hz, $J_{6H,1'Ha}$ = 6.3 Hz, $J_{6H,1'Hb}$ = 3.5 Hz, 1 H, H-6), 3.51 (dd, $J_{1'Ha,Hb}$ = 11.5 Hz, $J_{6H,1'Ha}$ = 6.3 Hz, 1 H, Ha-1'), 3.71 (s, 3H, OMe), 3.81 (dd, $J_{6H,7H}$ = 9.7 Hz, $J_{7H,8H}$ = 9.1 Hz, 1 H, H-7), 3.94 (dd, $J_{1'Ha,Hb}$ = 11.5 Hz, $J_{6H,1'Hb}$ = 3.5

Hz, 1 H, Hb-1'), 4.08 (dd, $J_{7H,8H}$ = 9.1 Hz, $J_{8H,8aH}$ = 7.6 Hz, 1 H, H-8), 5.04 (dd, $J_{8H,8aH}$ = 7.6 Hz, $J_{4aH,8aH}$ = 4.4 Hz, 1 H, H-8a), 6.16 (dd, $J_{4aH,8aH}$ = 4.4 Hz, 1 H, H-4a), 7.11-7.82 (m, 4 H_{arom}). ^{13}C NMR (DMSO-d_6/TMS) δ: 26.6, 50.2, 51.7, 54.4, 62.8, 77.6, 85.9, 125.1, 127.2, 128.8, 133.2, 173.5, 192.0. Mass (*m/z*): 388 (MH^+). Anal. Calcd for $C_{15}H_{17}NO_5S_3$: C, 46.49; H, 4.42; N, 3.61%. Found: C, 46.68; H, 4.11; N, 3.24%.

Compound **15a:** R_f (15% EtOAc/hexane) 0.51. IR (KBr) υ_{max} 3347, 3321, 3010, 1684, 1599, 1583, 1458, 1057 cm^{-1}. ^{1}H NMR (DMSO-d_6 + D_2O/TMS) δ: 3.29 (ddd, $J_{6H,1'H}$ = 6.7 Hz, $J_{1'H,2'Ha}$ = 5.5 Hz, $J_{1'H,2'Hb}$ = 2.6 Hz, 1 H, H-1'), 3.46 (dd, $J_{6H,7H}$ = 9.9 Hz, $J_{6H,1'H}$ = 6.7 Hz, 1 H, H-6), 3.57 (dd, $J_{2'Ha,Hb}$ = 11.8 Hz, $J_{6H,1'Ha}$ = 5.5 Hz, 1 H, Ha-2'), 3.81 (dd, $J_{6H,7H}$ = 9.9 Hz, $J_{7H,8H}$ = 9.2 Hz, 1 H, H-7), 3.91 (dd, $J_{2'Ha,Hb}$ = 11.8 Hz, $J_{6H,1'Hb}$ = 2.6 Hz, 1 H, Hb-2'), 4.28 (dd, $J_{7H,8H}$ = 9.2 Hz, $J_{8H,8aH}$ = 7.2 Hz, 1 H, H-8), 5.01 (dd, $J_{8H,8aH}$ = 7.2 Hz, $J_{4aH,8aH}$ = 4.3 Hz, 1 H, H-8a), 6.25 (dd, $J_{4aH,8aH}$ = 4.3 Hz, 1 H, H-4a), 7.09-7.69 (m, 5 H_{arom}). ^{13}C NMR (DMSO-d_6/TMS) δ: 33.1, 41.8, 51.8, 70.4, 72.3, 77.2, 85.9, 126.3, 129.2, 131.8, 134.5, 173.9, 192.5. Mass (*m/z*): 388 (MH^+). Anal. Calcd for $C_{15}H_{17}NO_5S_3$: C, 46.49; H, 4.42; N, 3.61%. Found: C, 46.73; C, 4.29; N, 3.89%.

Compound **15b:** R_f (15% EtOAc/hexane) 0.56. IR (KBr) υ_{max} 3353, 3320, 3013, 1687, 1605, 1587, 1450, 1053 cm^{-1}. ^{1}H NMR (DMSO-d_6 + D_2O/TMS) δ: 3.31 (ddd, $J_{6H,1'H}$ = 6.3 Hz, $J_{1'H,2'Ha}$ = 5.8 Hz, $J_{1'H,2'Hb}$ = 2.9 Hz, 1 H, H-1'), 3.49 (dd, $J_{6H,7H}$ = 9.8 Hz, $J_{6H,1'H}$ = 6.3 Hz, 1 H, H-6), 3.53 (dd, $J_{2'Ha,Hb}$ = 11.6 Hz, $J_{6H,1'Ha}$ = 5.8 Hz, 1 H, Ha-2'), 3.86 (dd, $J_{6H,7H}$ = 9.8 Hz, $J_{7H,8H}$ = 9.1 Hz, 1 H, H-7), 3.89 (dd, $J_{2'Ha,Hb}$ = 11.6 Hz, $J_{6H,1'Hb}$ = 2.9 Hz, 1 H, Hb-2'), 4.25 (dd, $J_{7H,8H}$ = 9.1 Hz, $J_{8H,8aH}$ = 7.6 Hz, 1 H, H-8), 4.99 (dd, $J_{8H,8aH}$ = 7.6 Hz, $J_{4aH,8aH}$ = 4.1 Hz, 1 H, H-8a), 6.21 (dd, $J_{4aH,8aH}$ = 4.1 Hz, 1 H, H-4a), 7.18-7.61 (m, 2 H_{arom}), 7.71-7.83 (m, 2 H_{arom}). ^{13}C NMR (DMSO-d_6/TMS) δ: 33.5, 41.3, 51.5, 70.9, 72.9, 77.5, 85.2, 126.5, 127.9, 133.8, 134.6, 173.2, 192.6. Mass (*m/z*): 422 (MH^+). Anal. Calcd for $C_{15}H_{16}ClNO_5S_3$: C, 42.70; H, 3.82; N, 3.32%. Found: C, 42.59; C, 3.91; N, 3.61%.

Compound **15c:** R_f (15% EtOAc/hexane) 0.46. IR (KBr) υ_{max} 3350, 3318, 3017, 1681, 1601, 1580, 1455, 1051 cm^{-1}. ^1H NMR (DMSO-d_6 + D_2O/TMS) δ: 3.28 (ddd, $J_{6H,1'H}$ = 6.4 Hz, $J_{1'H,2'Ha}$ = 5.3 Hz, $J_{1'H,2'Hb}$ = 2.8 Hz, 1 H, H-1'), 3.43 (dd, $J_{6H,7H}$ = 9.7 Hz, $J_{6H,1'H}$ = 6.4 Hz, 1 H, H-6), 3.58 (dd, $J_{2'Ha,Hb}$ = 11.9 Hz, $J_{6H,1'Ha}$ = 5.3 Hz, 1 H, Ha-2'), 3.67 (s, 3H, OMe), 3.88 (dd, $J_{6H,7H}$ = 9.7 Hz, $J_{7H,8H}$ = 9.3 Hz, 1 H, H-7), 3.85 (dd, $J_{2'Ha,Hb}$ = 11.9 Hz, $J_{6H,1'Hb}$ = 2.8 Hz, 1 H, Hb-2'), 4.29 (dd, $J_{7H,8H}$ = 9.3 Hz, $J_{8H,8aH}$ = 7.5 Hz, 1 H, H-8), 4.96 (dd, $J_{8H,8aH}$ = 7.5 Hz, $J_{4aH,8aH}$ = 4.4 Hz, 1 H, H-8a), 6.22 (dd, $J_{4aH,8aH}$ = 4.4 Hz, 1 H, H-4a), 7.03-7.81 (m, 4 H_{arom}). ^{13}C NMR (DMSO-d_6/TMS) δ: 32.9, 41.7, 51.2, 54.3, 70.6, 72.6, 77.8, 85.3, 126.8, 128.4, 130.5, 134.5, 173.5, 192.9. Mass (*m/z*): 418 (MH^+). Anal. Calcd for $C_{16}H_{19}NO_6S_3$: C, 46.03; H, 4.59; N, 3.35%. Found: C, 46.31; C, 4.29; N, 3.21%.

Procedure for isolation of intermediate 9a (*n*=3, Ar=Ph) and 12a (*n*=3, Ar=Ph) and their cyclization into corresponding thiazines 7a and 14a.

The procedure followed was the same as described above for the synthesis of **7a** and **14a** except that the time of stirring in this case was 4.5 h instead of **8h** for **7a** and 7.5 h for **14b**. The adducts **9a** and **12a** were purified by silica gel column chromatography (hexane-EtOAc, 8:2) to obtain an analytical pure sample of **9a** and **12a** in 46% and 49% yields respectively. A mixture of intermediates **9a** or **12a** (2.0 mmol) and [bmim]OH **5** (0.30 mmol) in 10 mL THF was stirred at room temperature for next 4h to give the corresponding product **7a** and **14a** quantitatively and was isolated and purified in the same way as described above for the compounds **7a** and **14a**. The ionic liquid [bmim]OH was also recovered by following the same procedure as described in case of above compounds **7a** and **14a**.

Compound **9a**: IR (KBr) υ_{max} 3348, 3018, 1770, 1605, 1588, 1455, 1058 cm^{-1}. ^1H NMR (DMSO-d_6 + D_2O/TMS) δ: 3.48 (dd, $J_{2'H,\ 3'H}$ = 4.3 Hz, $J_{1'H,\ 2'H}$ = 6.8 Hz, 1 H, H-2'), 3.59 (ddd, $J_{2'H,\ 3'H}$ = 4.3 Hz, $J_{3'H,\ 4'Ha}$ = 5.8 Hz, $J_{3'H,\ 4'Hb}$ = 3.1 Hz, 1 H, H-3'), 3.73 (dd, $J_{3'H,\ 4'Ha}$ = 5.8 Hz, $J_{4'Ha,\ 4'Hb}$ = 10.6 Hz, 1 H, Ha-4'), 3.98 (dd, $J_{NCH,SCH}$ = 4.2 Hz, $J_{SCH,1'H}$ = 5.5 Hz, 1 H, SCH), 4.09 (dd, $J_{1'H,\ 2'H}$ = 6.8 Hz, $J_{1'H,\ SCH}$ = 5.5 Hz,

1 H, H-1'), 4.27 (dd, $J_{3'H,\ 4'Hb}$ = 3.1 Hz, $J_{4'Ha,\ 4'Hb}$ = 10.6 Hz, 1 H, Hb-4'), 5.81 (d, $J_{NCH,SCH}$ = 4.2 Hz, 1 H, NCH), 7.13–7.71 (m, 10 H_{arom}). ^{13}C NMR (DMSO-d_6/TMS) δ: 38.7, 52.3, 67.5, 70.2, 71.8, 74.4, 92.4, 125.1, 126.2, 127.9, 128.8, 129.5, 130.2, 135.9, 138.3, 173.9, 192.5. Mass (*m/z*): 463 (MH^+). Anal. Calcd for $C_{21}H_{22}N_2O_6S_2$: C, 54.53; H, 4.79; N, 6.06%. Found: C, 54.81; C, 4.47; N, 6.28%.

Compound **12a**: IR (KBr) υ_{max} 3351, 3013, 1773, 1601, 1585, 1451, 1053 cm^{-1}. ^{1}H NMR (DMSO-d_6 + D_2O/TMS) δ: 2.26 (s, 3 H, Me), 3.43 (dd, $J_{2'H,\ 3'H}$ = 4.1 Hz, $J_{1'H,\ 2'H}$ = 6.4 Hz, 1 H, H-2'), 3.56 (ddd, $J_{2'H,\ 3'H}$ = 4.1 Hz, $J_{3'H,\ 4'Ha}$ = 5.8 Hz, $J_{3'H,\ 4'Hb}$ = 2.9 Hz, 1 H, H-3'), 3.79 (dd, $J_{3'H,\ 4'Ha}$ = 5.8 Hz, $J_{4'Ha,\ 4'Hb}$ = 10.9 Hz, 1 H, Ha-4'), 3.88 (dd, $J_{1'H,\ 2'H}$ = 6.4 Hz, $J_{SCHacyclic,1'H}$ = 5.5 Hz, 1 H, H-1'), 3.97 (dd, $J_{SCHcyclic,\ SCHacyclic}$ = 4.4 Hz, $J_{SCHacyclic,1'H}$ = 5.5 Hz, 1 H, $SCH_{acyclic}$), 4.09 (dd, $J_{3'H,\ 4'Hb}$ = 2.9 Hz, $J_{4'Ha,\ 4'Hb}$ = 10.9 Hz, 1 H, Hb-4'), 4.27 (d, $J_{SCHcyclic,\ SCHacyclic}$ = 4.4 Hz, 1 H, SCH_{cyclic}), 7.07–7.83 (m, 10 H_{arom}). ^{13}C NMR (DMSO-d_6/TMS) δ: 23.1, 38.5, 62.7, 68.1, 70.5, 72.2, 73.9, 125.5, 126.7, 128.3, 129.0, 130.5, 131.5, 132.2, 139.3, 168.1, 171.8 and 192.2. Mass (*m/z*): 496 (MH^+). Anal. Calcd for $C_{22}H_{25}NO_6S_3$: C, 53.31; H, 5.08; N, 2.83%. Found: C, 53.07; C, 5.21; N, 3.17%.

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Table 1. Optimization of reaction conditions for the formation of representative compound **7a**

Entry	Catalyst (mol %)	Solvent	Time (h)[a]	Yield (%)[b]
1	[Bmim]Br (15)	CH_3CN	8	52
2	[Bmim]Cl (15)	CH_3CN	8	46
3	[Bmim]PF_6 (15)	CH_3CN	8	49
4	[Bmim]Br (15)	MeOH	8	34
5	[Bmim]Br (15)	THF	8	59
6	[Bmim]Br (15)	1,4-Dioxane	8	56
7	[Emim]OH (15)	THF	8	74
8	[Mpim]OH (15)	THF	8	88
9	[Bmim]OH (15)	THF	8	92
10	[Bmim]OH (15)	CH_3CN	8	82
11	[Bmim]OH (15)	1,4-Dioxane	8	85
12	[Bmim]OH (15)	MeOH	8	72
13	[Bmim]OH (10)	THF	10	78
14	[Bmim]OH (20)	THF	8	93
15	-	THF	10	

[a] Time for completion of reaction at 90 ^{o}C (indicated by TLC).

[b] Yield of isolated and purified product **7a**.

Table 2 MW assisted synthesis of **7a**.

Entry	Catalyst System	MW	
		Time (min)[a]	Yield (%)[b,c]
1	$CeCl_3.7\ H_2O$	15	43
2	$CeCl_3.7\ H_2O$/NaI	13	51
3	K-10 clay	12	57
4	Silica gel	18	24
5	Neutral alumina	20	11
6	Acidic alumina	20	17
7	Basic alumina	20	
8	–	20	–

[a] Time for completion of the reaction at 90 ^oC.

[b] Yield of isolated and purified product **7a**.

[c] The product **7a** was characterized by IR, ^1H NMR, ^{13}C NMR and EIMS data.

Table 3 One-step synthesis of imino-/ and thiosugar annulated 1,3-thiazines **7**, **8** and **14** and **15**.

Entry	Product	Time (h)[a]	Ar	X	Yield (%)[b,c]	*cis:trans* ratio[d]
1	**7a**	8	Ph	NCOPh	93	97:03
2	**7b**	6.5	4-ClC_6H_4	NCOPh	93	95:05
3	**7c**	8	4-$MeOC_6H_4$	NCOPh	84	98:02
4	**8a**	8	Ph	NCOPh	88	95:05
5	**8b**	7.5	4-ClC_6H_4	NCOPh	91	95:05
6	**8c**	8	4-$MeOC_6H_4$	NCOPh	89	97:03
7	**14a**	7.5	Ph	S	91	95:05
8	**14b**	8	4-ClC_6H_4	S	93	96:04
9	**14c**	8	4-$MeOC_6H_4$	S	90	98:02
10	**15a**	6.5	Ph	S	90	98:02
11	**15b**	7.5	4-ClC_6H_4	S	91	95:05
12	**15c**	7.5	4-$MeOC_6H_4$	S	90	97:03

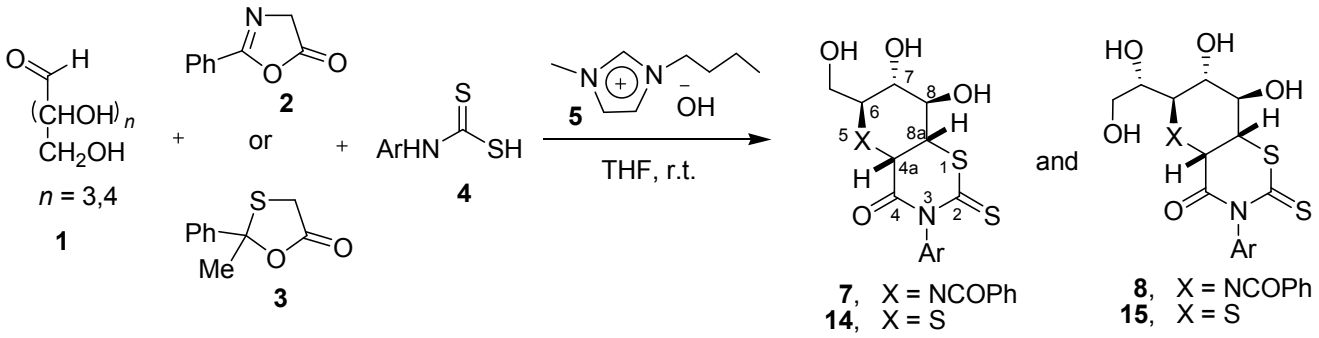
[a] Stirring time at room temperature.

[b] Yield of isolated and purified products.

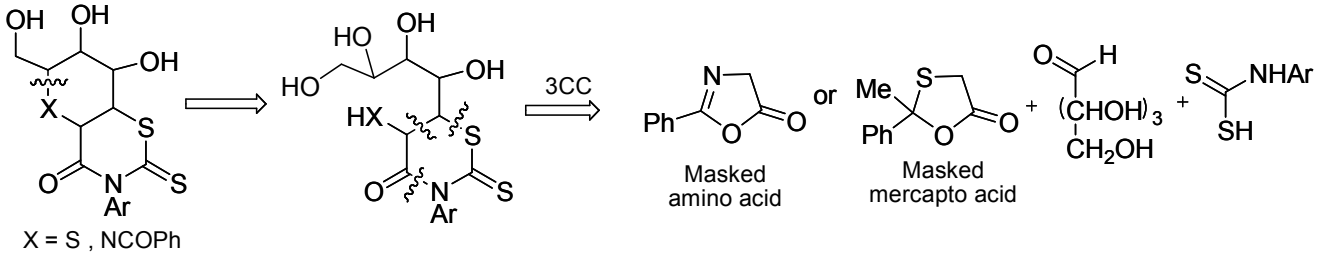
[c] All compounds gave C, H and N analyses within ± 0.37%, and satisfactory spectral (IR, ^{1}H NMR, ^{13}C NMR and EIMS) data.

Table 4 Recyclability of TSIL.

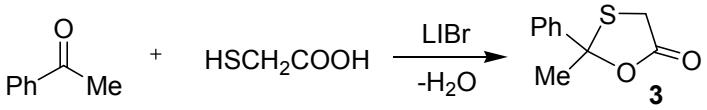
Table 3, Entry 1	Run 1	Run 2	Run 3	Run 4	Run 5
Yield (%)	93	93	92	92	91



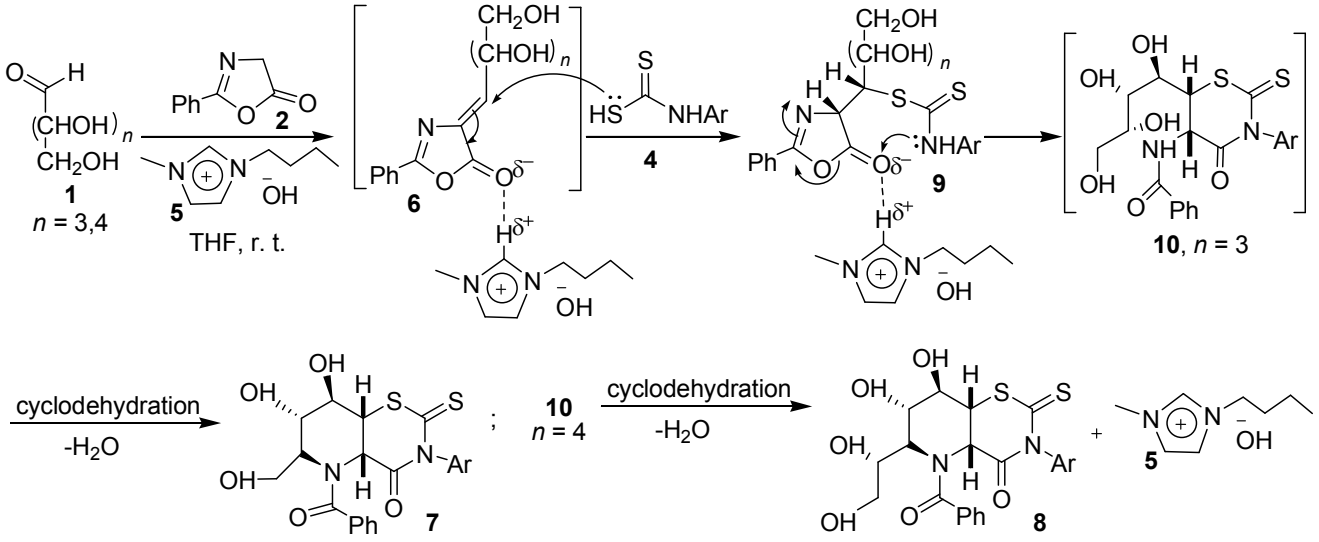
Scheme 1 Synthesis of imino-/ and thiosugar annulated 1,3-thiazines.



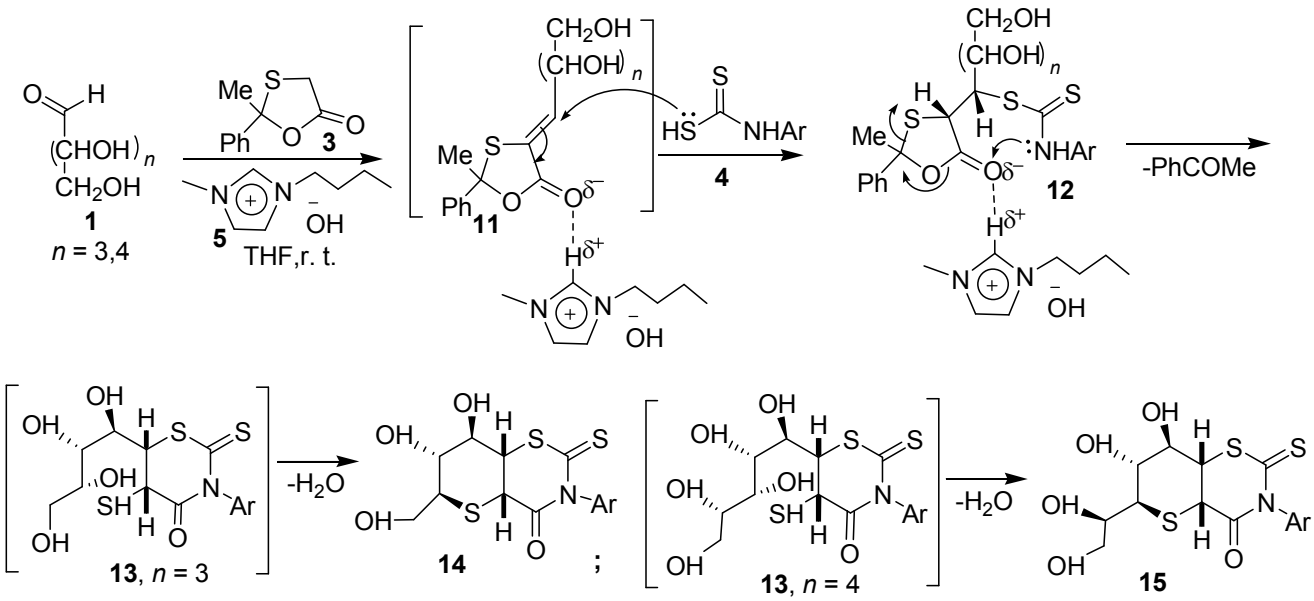
Scheme 2 Retro-synthetic scheme for the target compounds.



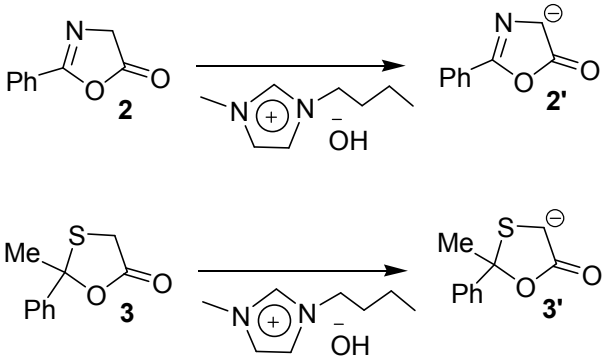
Scheme 3 Formation of masked mercapto acid **3**.[15]



Scheme 4 Plausible mechanism for the formation of iminosugar annulated 1,3-thiazines **7** and **8**.



Scheme 5 Plausible mechanism for the formation of thiosugar annulated 1,3-thiazines **14** and **15**.



Scheme 6 Role of [bmim]OH in Knoevenagel condensation.